Radiology

Workers with Libby Amphibole Exposure: Retrospective Identification and Progression of Radiographic Changes[1]

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Purpose: To assess how early pleural and/or parenchymal abnormalities consistent with asbestos exposure could be ascertained and to identify factors associated with progression.

Materials and Methods: Informed consent was obtained under an institutional review board–approved protocol. Multiple sequential chest radiographs obtained between 1955 and 2004 in 84 workers exposed to amphiboles associated with vermiculite in the town of Libby, Montana, were studied. A panel of three NIOSH B readers reviewed each worker's longitudinal chest radiograph series in reverse chronologic order and achieved a consensus reading for each radiograph. Measures of exposure were compared between workers with and those without progression of parenchymal and pleural abnormalities.

Results: Because of the way the study was designed, all subjects had pleural ($n = 84$) and/or parenchymal ($n = 26$) abnormalities on the most recent chest radiograph. Compared with other investigations that used different methods, this investigation revealed shorter latency periods (defined as the interval between date of hire and date of earliest radiographic detection) for circumscribed pleural plaque (median latency, 8.6 years) and pleural calcification (median latency, 17.5 years). Pleural abnormalities progressed in 64 workers, while parenchymal abnormalities progressed in 14. No significant differences were found with regard to measures of exposure between workers with and those without progression.

Conclusion: The latency period for the development of pleural plaques may be shorter than previously reported. Early plaques are subtle and may not be detectable except at retrospective review.

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L ibby, Montana, was the site of a vermiculite mining and processing facility that operated from the 1920s through 1990. Excesses in morbidity and mortality consistent with asbestos exposure have been documented among former Libby vermiculite workers (1,2). An increased prevalence of radiographic pleural changes has also been observed among household contacts of former workers and area residents (3,4). These findings have been attributed to exposure to an asbestiform mineral, frequently referred to as tremolite, in Libby vermiculite ore (5–7). However, the fibers composing this mineral, referred to here as Libby amphibole, may be better classified, in decreasing order of abundance, as winchite, richterite, and tremolite (5–7).

Series of chest radiographs belonging to a subset of vermiculite workers surfaced more than 10 years after the Libby operation closed. These radiograph series allow examination of the time course of asbestos-related abnormalities. The objectives for this study were to assess how early pleural and/or parenchymal abnormalities consistent with asbestos exposure could be ascertained and to identify factors associated with progression.

Materials and Methods

Study Population

Informed consent was obtained under a protocol approved by the Institutional Review Board of the Centers for Disease Control and Prevention. Using vital status information for each worker collected by the Agency for Toxic Substances and Disease Registry (ATSDR) for its Tremolite Asbestos Registry, we obtained consent from living workers to review their radiographs, and the Institution-

Advance in Knowledge

- Patients with exposure to Libby amphibole develop asbestos-related pleural disease earlier than is typically reported with asbestos exposure.

al Review Board of the Centers for Disease Control and Prevention approved the review of radiographs of deceased workers. The investigating team was then provided access to all available historical chest radiograph series belonging to a subset of the Libby vermiculite worker cohort. The majority of these radiographs, dating from 1955 to 2004, were collected by the local hospital as part of the bygone occupational screening program for the vermiculite mining and processing operation. They were recently archived by the Center for Asbestos Related Disease in Libby when Saint John's Lutheran Hospital proposed discarding them because of a lack of storage space. When more recent chest radiographs obtained for a clinical purpose were available, they were added to the occupational screening radiograph series. For this study, we included only those workers with at least two historical posteroanterior-view radiographs spanning a period of at least 4 years. No other series of radiographs from the local hospital for the remaining Libby worker cohort was available for review. The length of the radiographic observations in this data set is unique because of the retention of radiographs by local health facilities in a small community and because many of the workers were lifelong residents of Libby.

Previously, the ATSDR recreated the Libby vermiculite worker cohort (n = 1862). Within this population, historical serial radiographs were available for 184 (9.9%) workers; of these 184 workers, 88 met our inclusion criteria and 96 were excluded. Of the workers eligible for inclusion, 45 (51%) were deceased. Compared with the entire cohort and with workers excluded from the study, eligible subjects worked longer, had greater cumulative fiber exposure (CFE), and were older when hired (Table 1); therefore, they were not representative of the entire cohort.

Radiograph Evaluation

A panel of three board-certified, university-based thoracic radiologists (J.W.G., C.A.M., and R.D.T.), all with National Institute of Occupational Safety and

Health B reader certification, was assembled. The radiograph analysis consisted of two phases: (a) independent review of the most recent radiograph within a series and (b) panel consensus about the entire radiograph series. In the first phase, all three readers independently evaluated the most recent radiograph in each worker by using the 1980 International Labor Office (ILO) Classification of Radiographs of Pneumoconiosis (8). If all three readers independently identified pleural and/or parenchymal changes consistent with asbestos exposure, that radiograph series was accepted for evaluation in the panel consensus review. In the second phase, all three readers worked together simultaneously as a team to perform a consensus analysis of every radiograph on a retrospective basis. Beginning with the most recent radiograph, the panel categorized each posteroanterior chest radiograph in reverse chronologic order and reached a consensus regarding the type and degree of radiographic change. Panel members were required to agree about the type and presence of abnormalities before proceeding to the next, older radiograph. Disagreements were resolved by reviewing the next-most-recent radiograph and by tracking the abnormality retrospectively on older radiographs. ILO forms were completed for each radiograph that demonstrated a change in the scores of pleural and/or parenchymal abnormalities (sections

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Table 1

Characteristics of Original ATSDR Libby Vermiculite Worker Cohort and the Subcohort Examined in the Present Study

Group	No. of Workers*	Age at Hire (y)	Length of Employment (y)	CFE (fiber/mL-years)	Year of Hire
Entire cohort	1862 (100)	27.4 (22.1–36.7)	0.8 (0.1–4.1)	4.3 (0.8–22.5)	1958 (1947–1971)
All workers with stored radiographs	184 (9.9)	27.7 (22.3–33.7)	5.9 (1.6–15.9)	5.7 (0.4–52.1)	1974 (1960–1978)
Workers with insufficient no. of radiographs or length of follow-up	76 (4.1)	25.8 (22.5–31.3)	2.0 (0.4–3.8)	0.9 (0.1–6.1)	1978 (1972–1980)
Workers who declined to participate	20 (1.1)	24.1 (19.0–32.5)	3.9 (0.4–9.5)	1.0 (0.1–4.3)	1977 (1974–1980)
Available study subjects	88 (4.7)	31.6 (23.3–38.9)	15.6 (6.9–23.7)	42.4 (6.1–237.5)	1966 (1954–1974)

Note.—Unless otherwise specified, data are medians, with 25th–75th percentile ranges in parentheses.

* Data in parentheses are percentages.

2 and 3 of the ILO classification) in comparison to radiographs previously reviewed. The radiograph series were evaluated during two 5-day meetings separated by 9 months. About half the series were evaluated (with both phases of review) at each meeting. The radiograph series were manually shuffled to present them in random order to the readers in both the independent and consensus reviews.

Among the 88 eligible radiograph series, 84 were accepted for inclusion at the completion of the phase 1 review. The four excluded cases included those of three workers for whom no unanimous readings were achieved regarding the most recent radiograph and that of one worker with no radiographic abnormalities during 8 years of follow-up. A total of 1272 radiographs (mean number per worker, 15.1 ± 7.8 [standard deviation]; range, two to 38) and 1811.2 years of radiographic follow-up (mean length of follow-up per worker, 21.6 years ± 8.2; range, 4.1–44.9 years) were evaluated in phase 2. The radiographs for which ILO forms were completed (n = 435) were given an ILO technical quality classification as follows: 87% (n = 380) good, 11% (n = 49) acceptable with no technical defect, 1% (n = 5) acceptable with some technical defect, and 0.2% (n = 1) unacceptable for classification purposes. The baseline posteroanterior chest radiograph for 10 workers was obtained more than 1 year before hire. For 41 workers, their initial chest radiograph was obtained more than 1 year after

hire, and for 21 workers, their initial radiograph was obtained more than 10 years after hire.

Assessment of Progression

Modifying the method used by Bourbeau et al (9), we created a semiquantitative index of pleural abnormality for each radiograph. Using the data from section 3 of the ILO forms, we converted the width category (A, B, or C) of each in-profile circumscribed pleural plaque and/or diffuse pleural thickening to a numeric score (1, 2, or 3, respectively). We then multiplied each width by its respective in-profile extent (1, 2, or 3) and added any en face extent (1, 2, or 3). For our index, we summed these results with any pleural calcification extent (1, 2, or 3 each for the diaphragm, chest wall, or other sites). Finally, scores in the right and left hemithoraces were summed, giving a range of possible scores from 0 to 66 for each radiograph.

We defined progression of pleural abnormalities as an increase of five points on this index or a change from no pleural abnormalities to the presence of any pleural change. Progression of parenchymal abnormalities was defined as an increase in at least one major profusion category (eg, from a score of 0 to 1, from a score of 1 to 2).

Statistical Analysis

We created survival curves to graphically represent the onset of radiographic changes, and we compared covariates between workers with and those without progression of pleural and/or parenchymal abnormalities. These vari-

ables included lifetime CFE (as fiber/mL-years), employment duration, year of hire, age at hire, and smoking history (as pack-years). Multiple logistic regression analysis was used to evaluate the effect of covariates on radiographic progression. For each worker, we created dichotomous dependent variables for the presence of progression of pleural and parenchymal abnormalities. Independent variables included in each model were lifetime CFE, employment duration, year of hire, and age at hire. CFE, an estimate of lifetime fiber exposure, was obtained from employment records; the methods used to estimate CFE are described elsewhere (10). Briefly, historical air sampling data were used to estimate the 8-hour time-weighted average (TWA) fiber exposure for all areas of the vermiculite operation by year. The proportion of each day spent at each location was calculated for each job title, and an 8-hour TWA exposure was estimated for each job at a given time. The CFE for each job that a worker held was estimated by weighting the 8-hour TWA exposure for a given job held by the worker by the length of time (in years) spent at that job. Finally, lifetime CFE for each worker was estimated by summing the CFE for each job that the worker held. Smoking history was available from company records for 58 (69%) of the 84 workers included in the phase 2 review; logistic regression models were also created for the subset of workers with available smoking data. Because CFE did not have a normal distribution, we used the median as the measure

Table 2

Characteristics of Study Subcohorts with Pleural (n = 84) and Parenchymal (n = 26) Changes

Abnormality	No. of Workers	Interval from Hire to Initial Change (y)	Age at Hire (y)	CFE (fiber/mL-years)	Length of Employment (y)	Year of Hire
Circumscribed pleural plaque	83	8.6 (1.4–14.7)	30.2 (23.2–37.2)	44.1 (6.5–238.5)	15.4 (6.9–24.3)	1965 (1953–1974)
Any pleural calcification	37	17.5 (8.1–24.2)	29.1 (22.8–34.7)	76.5 (19.9–324.0)	20.7 (9.9–26.8)	1957 (1946–1968)
Diffuse pleural thickening	12	27.0 (10.7–29.8)	33.4 (26.0–45.6)	317.8 (38.7–673.7)	21.6 (15.3–25.0)	1954 (1949–1962)
Profusion category ≥ 1/0	26	18.9 (13.9–26.8)	31.6 (26.4–34.8)	235.7 (67.0–724.6)	22.4 (16.3–28.2)	1954 (1947–1967)
Profusion category progression to ≥ 2/1	9	33.3 (24.4–34.1)	27.7 (26.4–33.4)	678.4 (116.8–1819.4)	25.4 (16.9–28.6)	1948 (1947–1951)
Profusion category progression to ≥ 3/2*	2	36.9 (35.6–38.1)	29.9 (26.4–33.4)	1303.4 (31.7–2575.2)	15.0 (1.4–28.6)	1946 (1945–1947)

Note.—Unless otherwise specified, data are medians, with 25th–75th percentile ranges in parentheses. Abnormality groups are not mutually exclusive.

* Because there are only two workers in this category, data are means, with ranges in parentheses.

of central tendency for all covariates. For comparing medians between two groups, we used the Wilcoxon rank-sum test. For all statistical analyses, we used software (SAS, version 9; SAS Institute; Cary, NC) (11). A P value of less than .05 was considered to indicate a significant difference.

Results

Radiographic Abnormalities

Table 2 shows the characteristics of the 84 workers with pleural and parenchymal changes. All but one had circumscribed pleural plaque, with a median latency (interval between hire date and earliest detection) of 8.6 years. Pleural calcification occurred in 37 (44%) workers, with a median latency of 17.5 years, and 12 (14%) workers had diffuse pleural thickening, with a median latency of 27.0 years. Parenchymal changes with a small opacity profusion category of 1/0 or greater occurred in 26 (31%) workers, with a median latency of 18.9 years. The profusion category progressed to 2/1 or greater in nine workers, and of these nine workers, two showed progression to 3/2 or greater. Among the 26 workers with parenchymal changes, 24 (92%) had only linear irregular opacities (ILO shape and size "s," "t," or "u") while two had regular opacities (ILO shape and size "p," "q," or "r").

Table 2 also summarizes the variation in median CFE for specific radiographic changes. Median CFE was great-est among workers with parenchymal abnormalities progressing to major profusion category 2 or 3, at 678.4 and 1303.4 fiber/mL-years, respectively. Workers with diffuse pleural thickening had the next highest CFE, at 317.8 fiber/mL-years, followed by those with major profusion category 1 parenchymal abnormalities (235.7 fiber/mL-years), pleural calcification (76.5 fiber/mL-years), and circumscribed pleural plaque (44.1 fiber/mL-years). These results are consistent with those in previously published literature regarding exposure-response relationships (12).

The survival curves show the percentage of workers without radiographic changes as a function of time and illustrate the latencies between hire date and the earliest detectable change. For parenchymal changes, the survival curves shift to the right (ie, latencies increase) with increasing profusion and show the time required to progress between profusion categories (Fig 1). Parenchymal changes were not detected in radiographs obtained within 10 years of hire. The survival curves for pleural changes show increasing latencies for circumscribed pleural plaque, calcification, and diffuse pleural thickening, respectively (Fig 2). Notably, eight workers had circumscribed pleural plaque when hired, and of these, two also had pleural calcification.

Radiographic Progression

Among workers with pleural (n = 84) or parenchymal (n = 26) changes, 64 (76%) and 14 (54%), respectively, met our definition of progression. CFE, hire year, years worked, and age at hire were not significantly different from those among workers without progression, and the multivariate logistic regression models did not yield significant results. Among workers with available smoking data, we obtained similar results. Controlling for age, increasing pleural calcification extent was associated with increased risk of progression (odds ratio: 2.1; 95% confidence interval: 0.7, 6.5), as was increasing circumscribed pleural plaque width (odds ratio: 3.5; 95% confidence interval: 1.2, 10.2).

Among workers with progressive pleural abnormalities, we calculated the median time to change from normal to mild (semiquantitative pleural abnormality index of 1–5), mild to moderate (index of 6–15), and moderate to severe (index > 15) disease. The median time from hire date to abnormality development was 11.5 years for mild pleural abnormalities (n = 54), 24.0 years for moderate abnormalities (n = 50), and 28.1 years (n = 12) for severe abnormalities. We also calculated the interval between hire date and change in in-profile circumscribed pleural plaque width from less than 5 to 5–10 mm or greater (ie, change in ILO pleural width category from A to B). Thirty-eight workers exhibited this increase, with a median latency of 17.6 years (25th–75th percentile range, 12.5–26.8 years). Only three workers had circumscribed pleural thickening
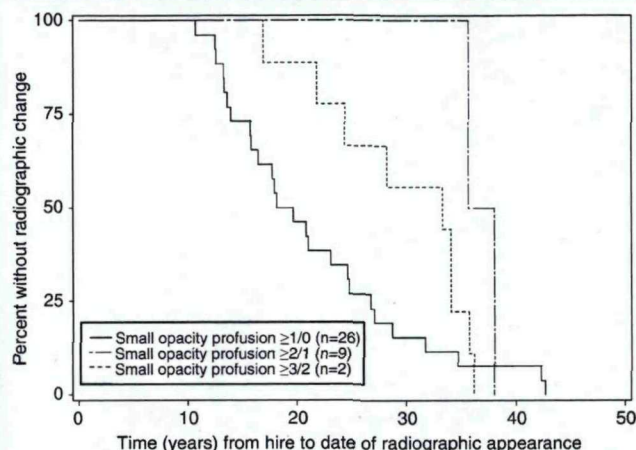
Figure 1

Figure 1: Plot of survivor function for the appearance of small-opacity major profusion categories after date of hire for workers with parenchymal abnormalities. Workers with profusion categories of 3/2 or greater represent a subset of those with profusion categories of 2/1 or greater, who in turn represent a subset of those with profusion categories of 1/0 or greater.
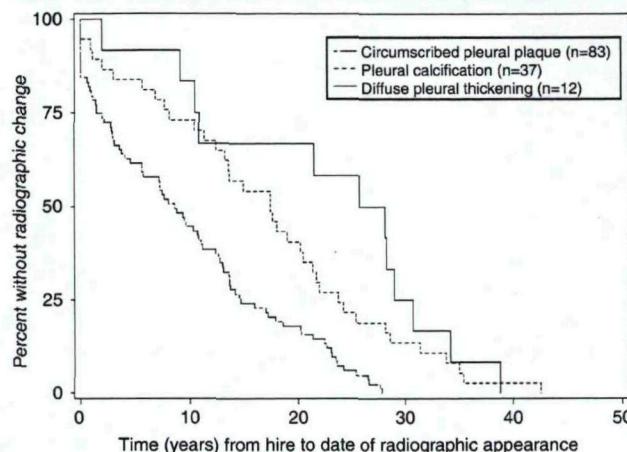
Figure 2

Figure 2: Plot of survivor function for the appearance of pleural plaques, diffuse pleural thickening, and pleural calcification after date of hire.
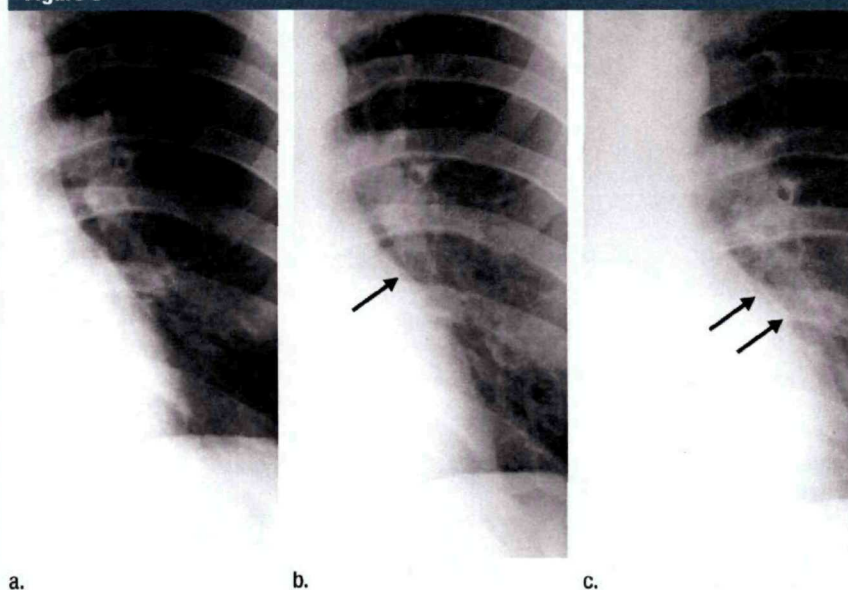
Figure 3

a.   b.   c.

Figure 3: Retrospective detection, on posteroanterior radiographs, of circumscribed pleural plaque that later became calcified. **(a)** This male worker's initial radiograph, obtained at age 24 years, is normal. **(b)** In an image obtained in the worker at 30 years of age, there is a straightening of the left heart border in the area of the left atrial appendage (arrow) consistent with noncalcified circumscribed pleural plaque. **(c)** In a radiograph obtained in the worker at 34 years of age, new calcification in the plaque (arrows) can be seen. The consensus panel noted that the changes in **b** were only detectable in retrospect.

with width greater than 10 mm (ie, ILO width category C), with a median latency of 32.3 years (range, 25–36 years).

Radiograph Examples

Figures 3–7 illustrate the type and natural history of the pleural changes observed. For many radiograph series, the readers believed that they were able to identify circumscribed pleural plaque retrospectively before it would have been identified in prospective evaluation; the pleural changes in Figures 3 and 4 typify those that could be identified only retrospectively with subsequent progression over time. Figure 5 shows images in a worker with rapid initial progression of diffuse pleural thickening. Figure 6 illustrates the progression of circumscribed pleural plaque to diffuse pleural thickening over decades. The latencies for calcification vary in Figures 3–6, which show calcification occurring 10, 27, 30, and 17 years after hire, respectively. Pre-employment radiographs were available for the worker in Figure 7. The panel observed circumscribed pleural plaque in a radiograph obtained when the worker was 9 years of age; this plaque progressed into the worker's adulthood.

Exposures Outside of Vermiculite Operation

Extensive nonoccupational amphibole exposure has been reported in Libby. In community-based screening conducted in Libby, a risk factor significantly associated with pleural abnormalities was living with a vermiculite worker (ie, household contact exposure) (3). Also,

a.   b.   c.   d.   e.
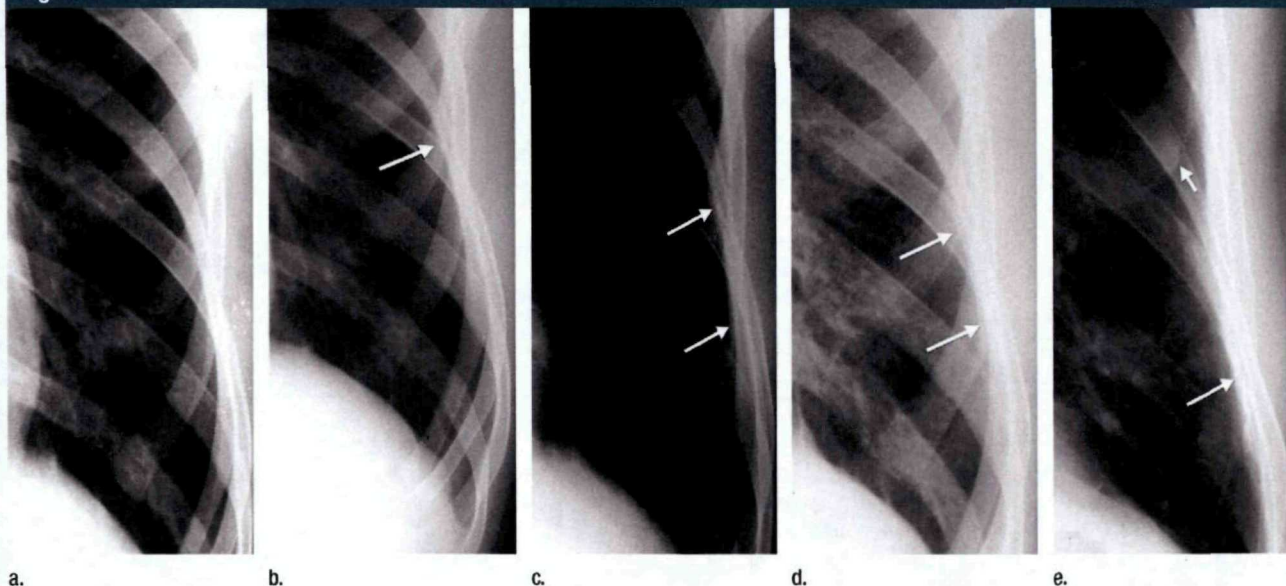
Figure 4:   Retrospective detection, on posteroanterior radiographs, of developing circumscribed pleural plaque with late calcification. **(a)** The initial chest radiograph in this male worker, obtained at age 21 years, is normal. **(b)** Five years later, minimal pleural thickening is visible next to the medial border of the left eighth rib (arrow; top arrow in **b**, **c**, and **d**). **(c)** Six years after the first examination, there is an additional pleural opacity medial to the left eighth rib (bottom arrow). **(d)** Seven years after the initial examination, there is unequivocal circumscribed pleural plaque medial to the left eighth rib (bottom arrow). **(e)** Twenty-seven years after the initial examination, there is increasing width and new calcification in the circumscribed pleural plaque (long arrow) with a new en face plaque (short arrow). The B reader consensus panel noted that the pleural thickening in **b** and **c** was not likely to be detected at independent prospective evaluation.

the prevalence of pleural abnormalities was associated with the number of nonoccupational exposure pathways (eg, gardening with vermiculite, playing on piles of vermiculite, and participation in recreational activities near the mine) (3). Using ATSDR data, we were able to examine potential exposures occurring outside of the vermiculite operation for 31 (37%) of the 84 subjects. From among these 31 workers, we identified 21 with household contact exposure, residence in Libby prior to being hired by the vermiculite operation, or employment in an occupation with potential asbestos exposure. We compared those workers with workers with no self-reported or unknown exposure histories ($n = 63$); the former had shorter median latencies from date of hire for the development of circumscribed pleural plaque (5.1 vs 9.4 years [$P = .5$]) and pleural calcification (11.3 vs 17.6 years [$P = .76$]). However, among 15 workers with circumscribed pleural plaque and latencies of fewer than 5 years, six had no self-reported ex-

posures that occurred outside of the vermiculite operation. The workers in Figures 3, 4, and 6 had no history of potential exposure outside of the vermiculite operation; this information was unavailable for the worker in Figure 5, and the worker in Figure 7 was the household contact of another vermiculite worker.

Discussion

It is generally accepted that asbestos-related circumscribed pleural plaque is radiographically detectable 20 years after initial exposure (13–17). This observation was also made in two studies (18,19) in which serial radiographs of workers were interpreted on a prospective basis and were used to quantify the latency of asbestos-related radiographic changes. In one of these studies (18), circumscribed pleural plaque was identified, on average, more than 31 years after initial exposure. In the other study (19), only 10% of subjects had circumscribed pleural plaque 10–19

years after initial exposure. Similarly, pleural calcification is radiographically detectable 30 years after initial exposure (13). Results of our investigation indicate that circumscribed pleural plaque and calcification may become evident on chest radiographs earlier than previously reported.

Our earlier detection of pleural abnormalities may be related to multiple factors. The retrospective method of this study increased the sensitivity for early circumscribed pleural plaque detection. Community exposure prior to employment and pleural response to the unique composition of asbestiform fibers in vermiculite compared with other more common asbestos fibers may also be factors.

An increased awareness of potential radiographic changes is expected when this retrospective review method is used. This fact was confirmed by members of the radiologist consensus reading panel, who acknowledged a lower threshold for scoring subtle pleural changes when there was unequivocal circumscribed
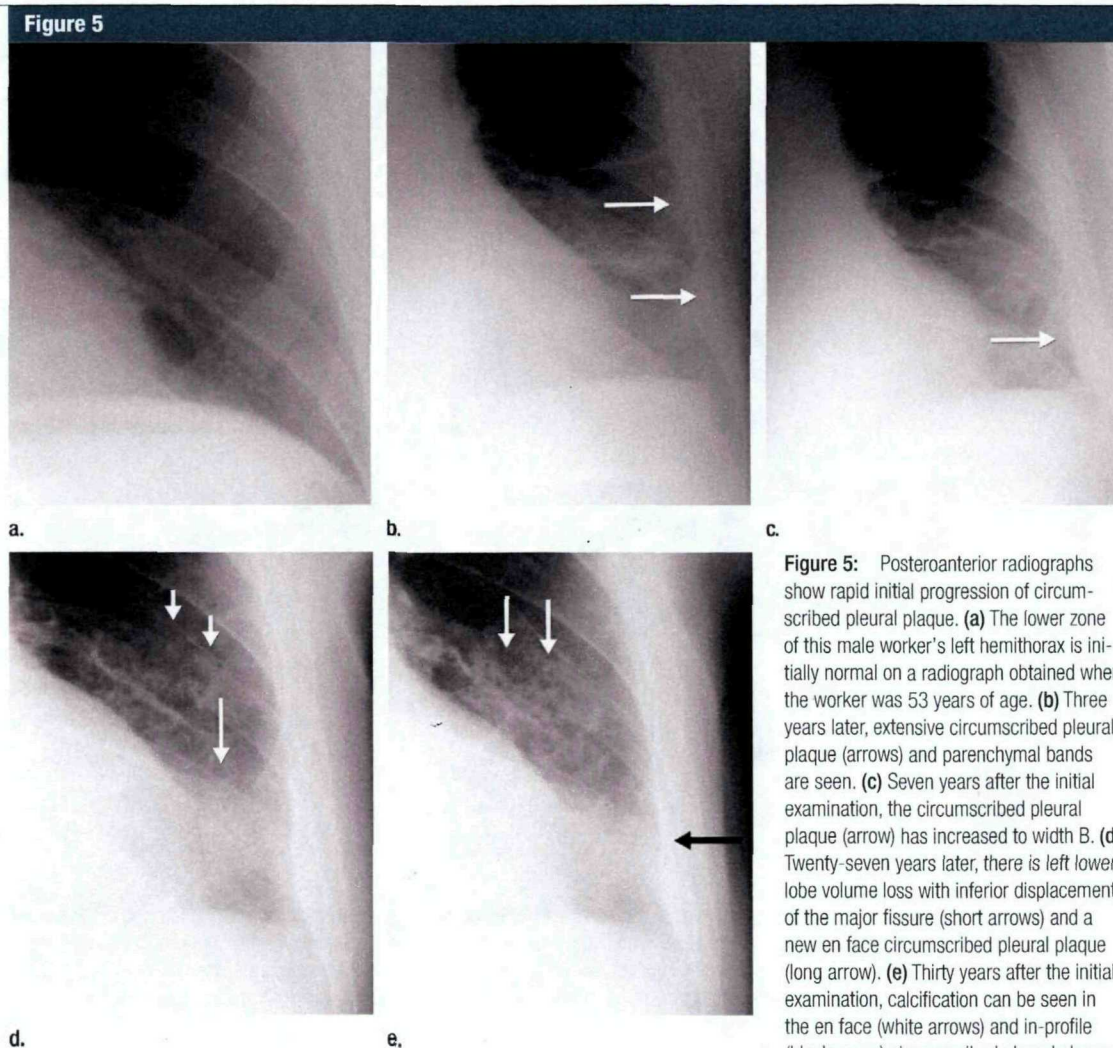
Figure 5: Posteroanterior radiographs show rapid initial progression of circumscribed pleural plaque. **(a)** The lower zone of this male worker's left hemithorax is initially normal on a radiograph obtained when the worker was 53 years of age. **(b)** Three years later, extensive circumscribed pleural plaque (arrows) and parenchymal bands are seen. **(c)** Seven years after the initial examination, the circumscribed pleural plaque (arrow) has increased to width B. **(d)** Twenty-seven years later, there is left lower lobe volume loss with inferior displacement of the major fissure (short arrows) and a new en face circumscribed pleural plaque (long arrow). **(e)** Thirty years after the initial examination, calcification can be seen in the en face (white arrows) and in-profile (black arrow) circumscribed pleural plaques.

pleural plaque at the same location on more recent radiographs from the radiographic series. These subtle pleural changes would not typically be classified as circumscribed plaque without the benefit of this retrospective review method.

The shortened latencies for circumscribed pleural plaque and calcification may also be due in part to community amphibole exposure that preceded the workers' employment at the vermiculite mining and processing facility. While conducting community screening in Libby, the ATSDR identified a high prevalence of self-reported nonoccupational amphibole exposures (3). In our study, we found clear evidence of the consequence of such exposure occurring out-

side of the vermiculite operation. In one individual, the panel retrospectively identified, on a radiograph obtained at age 9 years, a focal area of pleural calcification that enlarged over subsequent decades (Fig 7). Before working at the vermiculite facility, this individual was a lifelong Libby resident who lived with a parent who was a vermiculite worker. Health effects resulting from nonoccupational exposure to amphiboles have also been observed elsewhere. Among Turkish villagers living in structures whitewashed with tremolite and actinolite asbestos, the prevalence of pleural abnormalities is similar to that seen in cohorts with occupational exposure (20). Furthermore, among residents of Greece with nonoc-

cupational tremolite exposure, the average surface area of pleural thickening doubled at 15 years of follow-up (21).

Not all of the shortened latencies, however, could be explained by exposures that occurred outside of the vermiculite operation. This is illustrated by the finding of circumscribed pleural plaque with a latency of fewer than 5 years in six workers with no history of exposure to Libby amphibole or other asbestos prior to it being used by the vermiculite operation. The reduced latency for the occurrence of circumscribed pleural plaque may also reflect a unique pleural pathogenicity that has been associated with very low cumulative exposures to Libby amphibole (22).
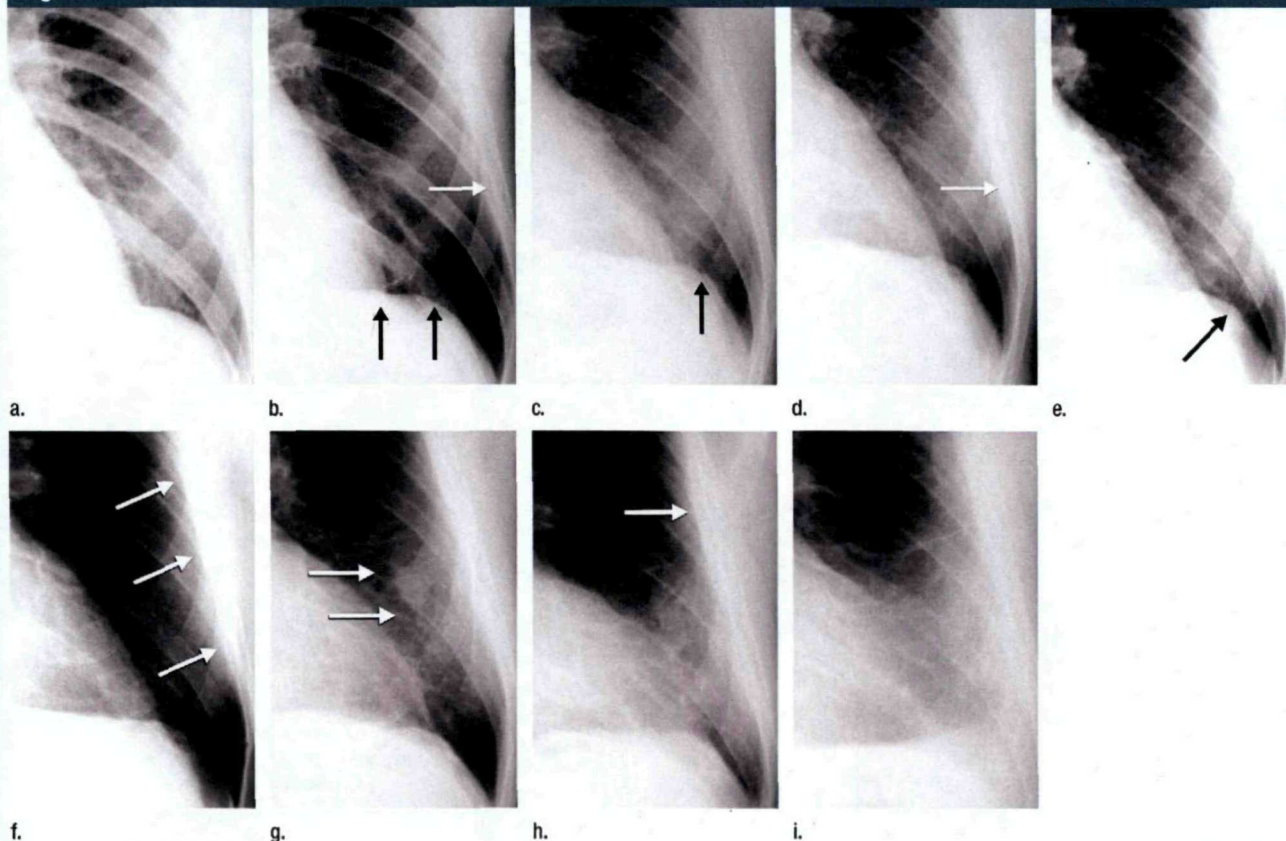
Figure 6:   Posteroanterior radiographs show 35-year progression of pleural abnormalities of the diaphragm and chest wall. **(a)** The left lung of this male worker is initially normal on a radiograph obtained when the worker was 25 years of age. **(b)** Seven years later, there is a small area of circumscribed pleural plaque of thickness A (white arrow) and mild, mesalike flattening of the diaphragm (black arrows). **(c)** Thirteen years after the initial radiograph, there is increased thickening of the diaphragmatic pleura (arrow). **(d)** Fifteen years after the initial radiograph, the circumscribed plaque along the wall (arrow) has increased to thickness B. **(e)** Seventeen years after the initial radiograph, there is calcification in the diaphragmatic plaque (arrow). **(f)** Twenty-two years after the initial radiograph, the chest wall plaque (arrows) has increased to extent 2. **(g)** Twenty-nine years after the initial examination, there is a new en face pleural plaque with calcification (arrows). **(h)** Thirty-one years after the initial examination, the calcification in the en face plaque and the lateral wall plaque (arrow) has increased. **(i)** Thirty-five years after the initial examination, costophrenic angle obliteration is present, suggesting diffuse pleural thickening.

None of the examined exposure variables were predictive of progressive pleural or parenchymal abnormalities. Other studies have revealed cumulative asbestos exposure (23–26), age (27,28), and exposure duration (24,27) to be predictive of progressive parenchymal changes. Within our study, the number of workers with parenchymal changes may have been too small to allow detection of significant differences between exposure groups. In instances of pleural thickening, cumulative chrysotile and crocidolite exposure has been reported to predict progression in one study (23), while other studies of workers exposed to amosite or crocidolite have not revealed a similar relationship (28–30). Circumscribed pleural plaque tends to be associated with a wide range of asbestos exposure levels, including exposures experienced by the general population, and such thickening is better related to latency than to cumulative exposure (15,17). Nonetheless, we found no significant difference with regard to latency or cumulative exposure between workers with and those without progression of pleural changes.

The risk of progression of pleural abnormalities was elevated with increasing pleural calcification extent and increasing width of circumscribed pleural plaque within a radiograph series. These radiographic findings may reflect increased specificity for pleural changes. Without such specificity, the panel may have had less confidence in recording the presence or progression of pleural changes. Factors that may decrease sensitivity to progression of pleural abnormalities include the use of categories of plaque thickness and the substantial alteration of the appearance of circumscribed pleural plaque that occurs with subtle changes in chest position when the radiograph is obtained.

Figure 7

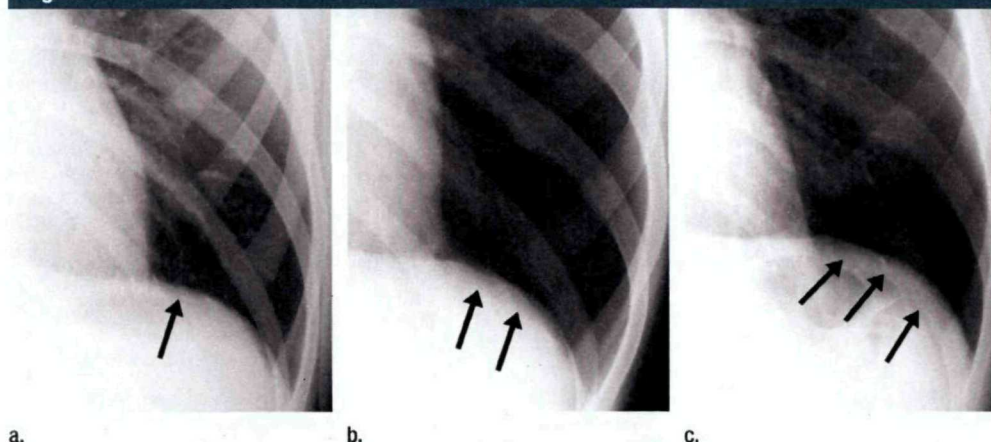a.   b.   c.

Figure 7: Posteroanterior radiographs show the appearance of diaphragmatic circumscribed pleural plaque in a boy with community amphibole exposure, demonstrating progression of this abnormality into early adulthood. **(a)** At age 9 years, there is a focal calcification on the left diaphragmatic pleura (arrow). **(b)** By age 17 years, a mesalike calcification is seen more laterally (arrows). **(c)** This mesalike calcification (arrows) has enlarged by age 25 years.

The retrospective method utilized in this study lowers the threshold for recognizing subtle pleural changes that subsequently progress to definite circumscribed pleural plaque consistent with asbestos exposure. These initial subtle changes, however, are unlikely to be recognized as consistent with asbestos exposure when one is interpreting isolated chest radiographs on a prospective basis; such an interpretation of subtle and ambiguous pleural findings would result in a high degree of sensitivity, but at the expense of specificity.

One limitation of this study was that the workers with the radiograph series were not representative of the entire worker cohort. Because of the way we designed the study, subjects were required to have radiographic abnormalities in their most recent radiograph, likely resulting in the inclusion of workers with greater CFE than the rest of the cohort. This fact increases the uncertainty of generalizing our results to the rest of the cohort or to other cohorts. Another weakness was the variation in the number of radiographs and length of radiographic follow-up among the radiograph series. This variation may have hindered our ability to detect radiographic progression. For example, workers without progressive pleural abnormalities had significantly fewer years between their first and last radiographs than did workers with such abnormalities (median, 17.7 vs 23.2 years; $P = .02$) and fewer radiographs (median, 12.5 vs 15.0; $P = .44$). Similarly, workers without progressive parenchymal abnormalities had fewer years between their first and last radiographs than did workers with such abnormalities (median, 21.1 vs 23.9 years; $P = .28$) and significantly fewer radiographs (median, 14.0 vs 20.5; $P = .02$). Finally, the readers may have introduced a learning bias to the data; as the readers gained experience with the study method, they may have been more likely to identify early radiographic changes. This may have resulted in misclassification of early radiographic change and may have resulted in an undercounting of workers with radiographic progression.

In summary, the median latency was 8.6 years for circumscribed pleural plaque and 17.5 years for pleural calcification. For those workers with progressive pleural changes, the median time for a change in ILO category for circumscribed pleural plaque was 17.6 years. Radiologists should be aware that asbestos-related pleural disease may be detectable earlier than previously described, even in a pediatric population. This has important implications for the natural history of asbestos-related disease and may have implications in regards to litigation and compensation.

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